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APPLICATION OF MULTICOMPONENT REACTIONS FOR CONSTRUCTION OF QUINOLINE DERIVATIVES

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Abstract: Camphor sulfonic acid (CSA) catalyzed diastereo selective synthesis of pyrano and furanoquinoline using ABB' type multi-component coupling of aryl amines with cyclic enol ether has been developed. Then in situ generated arylimine reacts with another molecule of electron rich olefines via 4+2 cycloaddition to give pyrano and furanoquinolines in good to excellent yield with high cis diastereoselectivity. Addition of water results in switching the diastereoselectivity towards trans.

Keywords: Pyranoquinoline, furanoquinoline, Camphor sulfonic acid, Cycloaddition, Organocatalyst.

Introduction:

The pyrano and furanoquinoline moieties are widely distributed in nature and reveal a broad range of biological activity. Pyranoquinolines are found in many alkaloids[I] such as veprisine, flindersine and orisine. Furanoquinoline are found in skimmianine and balfloxuridine alkaloid. These alkaloid exhibits important biological activities such as psychotropic[II] Antiallergic[III] anti-inflammatory[IV] and estrogenic activities[V]. Many synthetic methods have been developed for the synthesis of these compounds. The [4+2] cycloaddition reaction between N-arylimine and electron rich dienophile is probably the most powerful synthetic route for constructing N-containing six membered heterocyclic compounds. [VI] Various new synthetic methodologies have been reported for the synthesis of pyrano and furanoquinoline derivatives. Pyranoquinoline derivatives have been synthesized via aza-Diels-Alder reaction catalyzed by Lewis acid [VII-XII] metal triflates [XIII-XV] and protonic acids, such as HCl & trifluoroacetic acid. The aza Diels Alder reaction catalyzed by Lewis acid is the method of choice for the synthesis of pyrano/ furano-quinoline derivatives. However, many lewis acids are deactivated or some-times decomposed by nitrogen containing reactants. Lewis acids are trapped by nitrogen that's why more stoichiometric amount of lewis acid is required. Heterogeneous catalyst montmorillonite KSF [XVI] and cation exchange resin [XVII] have also been reported. More recently, Chao-Jun Li et.al. reported indium (III) chloride catalyzed synthesis of Pyranoquinoline in water[XVIII] and Johnson, et.al. reported a cation exchange resin catalysed synthesis of Pyranoquinolines [XIX] but these reagents lacks selectivity.

However, an *in situ* generated heterodiene is preferred over a preformed heterodiene because of heterodiens are unstable, hygroscopic and difficult to purify by column chromatography. In this light there is urgent need of an efficient, selective and facile protocol for the synthesis of these compounds. There are no re-ports on the synthesis of pyrano/furanoquinolines using organocatalyst. Camphor sulfonic acid is used in organic chemistry as acid catalyst and is involved in many different type of reaction such as nucleophiles promoted alkyne-iminium cyclisation,[XX] intramolecular opening of epoxides,[XXI-XXII] phenyl elation reaction,[XXIII] and spiroacetalization reaction.[XXIV-XXVI] We wish to report here a highly diastereoselective synthesis of pyrano/furanoquinolines by the reaction of aromatic amines with cyclic enol ether using camphor sulfonic acid as an organocatalyst at ambient temperature.

Experimental

The reactions were carried out at room temperature that is 28-32^{o}C. Unless otherwise specified, all the reagents were purchased from Sigma-Aldrich Chemical Co, Lan-caster and were used directly without further purification NMR spectra were obtained using the Brucker DPX 200 FT or Avance DRX 300MHz spectrometer Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Mass spectra were obtained using JEOL SX -102 (FAB+) instrument. Elemental analysis was performed using a Perkin Elmer Auto system XL Analyzer. Melting points were measured using a COM-PLAB melting-point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

Typical experimental procedure for the synthesis of Pyrano/furanoquinoline.

A mixture of substituted aniline (1mmol), cyclic enol ether (2mmol), and Camphor sulfonic acid (30 mol %) was taken in acetonitrile (5ml) stirred at room temperature for 4–6h. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and filtered and concentrated under vacuum The product was purified by silica gel column chromatography to afford the pure pyrano/ furanoquinoline derivatives. All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy.

Typical experimental procedure for the synthesis of Pyrano/furanoquinoline in biphasic system

A mixture of substituted aniline (1mmol), cyclic enol ether (2mmol), and Camphor sulfonic acid (30mol%) was taken in Acetonitrile-water (5ml 7:3) stirred at room temperature for 4–6h. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and filtered and concentrated under vacuum. The product was purified by silica gel column chromatography to afford the pure pyrano/furanoquinoline derivatives. All the products were characterized by 1H and 13C NMR spectroscopy.

Analytic data of synthesied compounds:

4-(3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano [3,2-c]quinoline-5-yl)butan-1-ol (3a, 4a). solid, mp 85–89°C **Compound 3a Cis-isomer:** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 - 1.70 (m, 10 H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.34 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.39 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3.60 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 4.98 (d, *J* = 5.7 Hz, 1 H), 6.38 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.67 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.96 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.31 (d, *J* = 7.5 Hz, 1 H, Ar-H) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.86, 22.14, 25.41, 31.96, 32.59, 35.52, 54.13, 60.63, 62.47, 72.41, 113.79, 117.74, 120.02, 127.51, 127.85, 145.01 ppm.

Compound 4a Trans-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 -1.70 (m, 10 H), 1.90 (m, 1 H), 3.58 (m, 1 H), 3.66 (m, 3 H), 3.90 (m, 1 H), 4.42 (d, *J* = 3.2 Hz, 1 H), 6.42 (d, *J* =

7.5 Hz, 1 H, Ar-H), 6.60 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.96 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.21 (d, *J* = 7.5 Hz, 1.H, Ar-H) ppm. MS (ES+): m/z = 262.2 $[M + 1]^+$. $C_{16}H_{23}NO_2$ (261.1729): calcd. C 73.53, H 8.87, N 5.36; found C 73.61,H 8.74, N 5.47.

R = p-OCH_3 4-(9- methoxy-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl)butan-1-ol (3b, 4b). Viscous oil.

Compound 3b Cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 -1.70 (m, 10H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.30 (dt, *J* = 2.6, 7.3 Hz, 1 H), 3.62 (m, 2 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 3.74 (s, 3 H, OCH_3), 5.00 (d, *J* = 5.4 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.66 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H), 6.90 (d, *J* = 2.6 Hz, 1 H, Ar-H) ppm.

Compound 4b Trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 - 1.70 (m, 10 H), 1.96 (m, 1 H), 3.48 (m, 1 H), 3.68 (m, 3 H), 3.72 (s, 3 H, OCH_3), 3.92 (m, 1 H), 4.44 (d, *J* = 5.4 Hz, 1 H), 6.50 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.68 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H), 6.80 (d, *J* = 2.6 Hz, 1 H, Ar-H) ppm. MS (ES+): m/z = 292 5 $[M + 1]^+$.

R = o-OCH_3 4-(7- methoxy-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl)butan-1-ol (3c, 4c). Solid, mp 52–59°C.

Compound 3c Cis-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1. 32–1.70 (m, 10 H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 2.10 (s, 3 H, CH_3), 3.30 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.38 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3 56 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.62 (t, *J* = 6.3 Hz, 2 H), 5.00 (d, *J* = 5.5 Hz, 1 H), 6.60 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.82 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.20 (d, *J* = 7.5 Hz, 1 H, Ar-H) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.47, 18.41, 21.23, 22.83, 24.02, 32.04, 32.91, 35.93, 49.64, 53.83, 62.16, 116.34, 119.45, 120.82, 128.73, 129.87, 142.30 ppm. MS (ES+): m/z = 292.2 $[M + 1]^+$. $C_{17}H_{25}NO_3$ (291.1834): calcd. C 70.07, H 8.65, N 4.81; found C 70.11, H 8.66, N 4.89.

R = o-CH_3 4-(7- methyl, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl) butan-1-ol (3d, 4d). Solid, mp 76–82°C

Compound 3d Cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1. 32–1. 70 (m, 10 H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 2.22 (s, 3 H, CH_3), 3.30 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.42 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3.58 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.62 (t, *J* = 6.3 Hz, 2 H), 5.00 (d, *J* = 5.7 Hz, 1 H), 6.40 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.82 (dd, *J* = 1.5, 7.5 Hz, 1 H, Ar-H), 7.18 (d, *J* = 1.5 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75MHz, $CDCl_3$): δ = 17.81, 20.56, 22.13, 25.38, 32.01, 32.77, 35.64, 54.26, 60.70, 62.48, 72.49, 114.03, 120.02, 127.03, 128.53, 129.67, 142.68 ppm.

Compound 4d Trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 – 1.70 (m, 10 H), 1.96 (m, 1 H), 2.20 (s, 3 H, CH_3), 3.58 (m, 1 H), 3.62 (m, 3 H), 3.96 (m, 1 H), 4.40 (d, *J* = 3.2 Hz, 1 H), 6.52 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.96 (dd, *J* = 1.5, 7.5 Hz, 1 H, Ar-H), 7.00 (d, *J* = 1.5 Hz, 1 H, Ar-H) ppm. MS (ES+): m/z = 276.0 $[M + 1]^+$. $C_{17}H_{25}NO_2$ (275.1885): calcd. C 74.14, H 9.14, N 5.09; found C 74.09, H 8.97, N 5.23.

R = p-F, 4-(9-flouro-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano [3,2-c]quinoline-5-yl)butan-1-ol (3e, 4e). Solid, mp 110–111°C.

Compound 3e Cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1. 32–1.70 (m, 10 H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.25 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.38 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3.56 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.62 (t, *J* = 6.3 Hz, 2 H), 4.97 (d, *J* = 5.4 Hz, 1 H), 6.42 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.70 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.10 (dd, *J* = 2.6, 7.5 Hz, 1H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.77, 22.14, 25.22, 31.90, 32.52, 35.18, 54.24, 60.84, 62.41, 72.18, 113.42, 113.60, 114.74, 114.81, 121.64, 141.18 ppm.

Compound 4e Trans isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 – 1.32 (m, 10 H), 1.90 (m, 1 H), 3.35 (m, 1 H), 3.48 (m, 1 H), 3.66 (m, 2 H), 3.86 (m, 1 H), 4.42 (d, *J* = 3.2 Hz, 1 H), 6.48 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.78 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.95 (dd, *J* = 2.6, 7.5 Hz, 1

H, Ar-H) ppm. MS (ES+): m/z = 280.5 $[M + 1]^+$. $C_{16}H_{22}FNO_2$ (279.1635): calcd. C 68.79, H 7.94, N 5.01; found C 68.86, H 7.86, N 5.21.

R = p-Cl, 4-(9- chloro-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl)butan-1-ol (3f, 4f). Solid, mp 115–117ºC.

Compound 3f Cis-isomer: 1H NMR (300 MHz, CDCl3): δ = 1.32–1.70 (m, 10 H), 2.02 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.34 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.50 (dt, *J* = 2.3, 11.4, 1 H), 3.65 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.70 (t, *J* = 6.3 Hz, 2 H), 5.00 (d, *J* = 5.5 Hz, 1 H), 6.42 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.96 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H), 7.30 (d, *J* = 2.6 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 17.87, 21.28, 22.68, 23.03, 24.10, 32.97, 36.09, 50.19, 66.67, 72.98, 115.33, 122.52, 123.50, 128.82, 129.53, 143.58 ppm.

Compound 4f Trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.32 – 1.70 (m, 10 H), 1.88 (m, 1 H), 3.50 (m, 1 H), 3.65 (m, 3 H), 3.86 (m, 1 H), 4.42 (d, *J* = 3.0 Hz, 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.98 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H,), 7.18 (d, *J* = 2.6 Hz, 1H, Ar-H) ppm. MS (ES+): m/z = 296.2 $[M + 1]^+$. $C_{16}H_{22}ClNO_2$ (295.1339): calcd. C 64.97, H 7.50, N 4.74; found C 64.87, H 7.78, N 4.65.

R = p-Br, 4-(9-bromo-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl)butan-1-ol (3g, 4g). Solid,mp 74–76°C.

Compound 3g Cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.32–1.70 (m, 10 H), 2.0 (m, 1 H), 3.36 (m, 1 H), 3.42 (m, 1 H), 3.60 (m, 1 H), 3.62 (m, 2 H), 4.98 (d, *J* = 5.5 Hz, 1 H), 6.38 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.04 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H), 7.42 (d, *J* = 2.6 Hz, 1 H, Ar-H) ppm.**Compound 4g Trans-isomer:** ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.32–1.70 (m, 10 H), 1.84 (m, 1 H), 3.46 (m, 1 H), 3.65 (m, 3 H), 3.86(m, 1 H), 4.40 (d, *J* = 3.0 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.10 (dd, *J* = 2.6, 8.0 Hz, 1 H, Ar-H), 7.30 (d, *J* = 2.6 Hz, 1 H, Ar-H) ppm. MS (ES+): m/z = 340.5 $[M + 1]^+$. $C_{16}H_{22}BrNO_2$ (339.0834): calcd. C 56.48, H 6.52, N 4.12; found C 56.65, H 6.84, N 3.87.

R = m-NO_2, 4-(8- nitro-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano[3,2-c]quinoline-5-yl)butan-1-ol (3h, 4h). Viscous oil.

Compound 3h Cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.32–1.70 (m, 10 H), 2.00 (dddd, *J* = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.10 (dt, *J* = 2.6, 7.3 Hz, 1 H), 3.32 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3.54 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 5.38 (d, *J* = 5.8 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.82 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.10 (s, 1 H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 17.81, 20.83, 23.72, 24.52, 32.32, 34.14, 53.62, 61.96, 62.26, 69.26, 112.55, 112.63, 118.54, 128.87, 146.05, 151.40 ppm.

Compound 4h Trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): 1. 32–1.70 (m, 10 H), 1.82 (m, 1 H), 3.36 (m, 1 H), 3.68 (m, 3 H), 3.88 (m, 1 H), 4.98 (d, *J* = 5.8 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.05 (s, 1 H, Ar-H) ppm. MS (ES+): m/z = 307.2 $[M + 1]^+$.

R = H,3-(2, 3, 3a, 4, 5, 9b–hexahydrofuro[3,2-c]quinolin-4-yl)propan-1-ol (3i, 4i). Viscous oil. **Compound 3(i) Cis-isomer:** ^{1}H NMR (300MHz, $CDCl_3$): *δ* = 1.55-1.90 (m, 5 H), 2.03 (m, 1 H), 2.64 (1 H, OH), 2.63 (m, 1 H), 3.44 (m, 1 H), 3.70 (m, 2 H), 3.79 (m, 2 H), 5.11 (d, *J* = 8.0 Hz, 1 H), 6.30 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.76 (m, 1 H, Ar-H), 7.04 (m, 1 H, Ar-H), 7.29 (d, *J* = 7.6 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75MHz, $CDCl_3$): *δ* = 24.22, 29.21, 30.93, 42.69, 52.68, 62.52, 66.81, 76.02, 114.86, 118.94, 122.84, 128.55, 130.25, 145.24 ppm.

Compound 4(i) Trans isomer: ^{1}H NMR (300MHz, $CDCl_3$): *δ* = 1.50-1.90 (m, 5 H), 2.20 (m, 1 H), 2.64 (1 H, OH), 2.82 (m, 1 H), 3.70 (m, 2 H), 3.79 (m, 2 H), 3.95 (m, 1 H), 4.56 (d, *J* = 5.6 Hz, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.09 (m, 1 H, Ar-H), 6.76 (m, 1 H, Ar-H), 7.34 (d, *J* = 7.6 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75MHz, $CDCl_3$): *δ* = 28.79, 29.37, 30.09, 41.39, 52.16, 62.64, 65.76, 76.10, 115.08, 118.42, 120.48, 129.10, 131.20, 145.16 ppm. MS (ES+): m/z = 234.0 $[M + 1]^+$.

R = p-Cl, **3-(8-chloro2, 3, 3a, 4, 5, 9b–hexahydrofuro[3,2-c]quinolin-4-yl)propan-1-ol (3j, 4j).** Viscous oil.

Compound 3(j) Cis-isomer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 1.97 (m, 1 H), 2.59 (m, 1 H), 2.90 (1 H, OH), 3.42 (m, 1 H), 3.70 (m, 2 H), 3.79 (m, 2 H), 5.03 (d, *J* = 8.0 Hz, 1 H), 6.44 (d, *J* = 8.4Hz, 1 H, Ar-H), 6.96 (dd, *J* = 2.4Hz, 8.4Hz, 1 H, Ar-H), 7.25 (d, *J* = 2.4Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75MHz, $CDCl_3$): δ = 24.01, 29.10, 30.88, 42.29, 52.37, 62.39, 66.91, 75.56, 112.86, 116.02, 124.09, 128.39, 129.66, 143.78 ppm.

Compound 4(j) Trans isomer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.19 (m, 1 H), 2.79 (m, 1 H), 2.90 (1 H, OH), 3.45 (m, 1 H), 3.70 (m, 2 H), 3.93 (m, 2 H), 4.50 (d, *J* = 5.6 Hz, 1 H), 6.55 (d, *J* = 8.4Hz, 1 H, Ar-H), 7.02 (dd, *J* = 2.8Hz, 8.8Hz, 1 H, Ar-H), 7.30 (d, *J* = 2.4Hz, 1 H, Ar-H) ppm.^{13}C NMR (75MHz, $CDCl_3$): δ = 28.72, 29.27, 30.03, 41.13, 52.17, 62.49, 65.80, 75.56, 116.22, 121.78, 122.26, 128.92, 130.59, 143.85 ppm. MS (ES+): m/z = 268.0 $[M + 1]^+$.

R = p-CH_3, 3-(8-methyl 2, 3, 3a, 4, 5, 9b–hexahydrofuro[3,2-c]quinoline-4-yl)propan-1-ol ((3k,4k). Viscous oil.

Compound 3(k) Cis-isomer: ^{1}H NMR (300MHz ,$CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.04 (m, 1 H), 2.23 (s, 3 H, CH_3), 2.62 (m, 1 H), 2.85 3.40 (m, 1 H), 3.70 (m, 2 H), 3.80 (m, 2 H), 5.08 (d, *J* = 8.0 Hz, 1 H), 6.46 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.86 (dd, *J* = 2.0 Hz, 8.0 Hz, 1 H, Ar-H), 7.11 (d, *J* = 2.0 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$):δ = 20.80, 24.28, 29.28, 30.97, 42.80, 53.00, 62.50, 66.89, 76.14, 115.00, 122.87, 128.17, 129.32, 130.51, 140.77 ppm.

Compound 4(k) Trans isomer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.20 (m, 1 H), 2.24 (s, 3 H, CH_3), 2.79 (m, 1 H), 3.70 (m, 2 H), 3.80 (m, 2 H), 3.95 (m, 1 H), 4.54 (d, *J* = 5.2 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz,1 H, Ar-H), 6.91 (dd, *J* = 2.0 Hz, 8.0 Hz,1 H, Ar-H), 7.17 (d, *J* = 2.0 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.73, 28.86, 29.45, 30.17, 41.65, 52.55, 62.65, 65.87, 76.14, 115.24, 120.74, 127.74, 129.81, 131.33, 142.77 ppm. MS (ES+): m/z = 248.2 $[M + 1]^+$.

R = p-OCH_3, **3-(8-methoxy 2, 3, 3a, 4, 5, 9b–hexahydrofuro [3,2-c]quinoline-4-yl)propan-1-ol 2 (3l, 4l).** Viscous oil.

Compound 3(l) Cis-isomer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.03 (m, 1 H), 2.62 (m, 1 H), 2.84 (1 H, OH), 3.38 (m, 1 H), 3.71 (m, 2 H), 3.75 (s, 3 H, OCH_3), 3.79 (m, 2 H), 5.07 (d, *J* = 8.0 Hz, 1 H), 6.52 (d, *J* = 8.8Hz, 1 H, Ar-H), 6.68 (dd, *J* = 2.8Hz, 8.4Hz, 1 H, Ar-H), 6.86 (d, *J* = 2.8 Hz, 1 H, Ar-H) ppm.^{13}C NMR (75MHz, $CDCl_3$): δ = 25 24, 29.10, 30.97, 42.67, 53.09, 55.90, 62.43, 66.90, 76.24, 114.05, 115.76, 116.18, 123.72, 139.31, 152.90 ppm.

Compound 4(l) Trans isomer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.23 (m, 1 H), 2.77 (m, 1 H), 3.71 (m, 2 H), 3.75 (s, 3 H, OCH_3), 3.79 (m, 2 H), 3.96 (m, 1 H), 4.56 (d, *J* = 5.6 Hz, 1 H), 6.65 (d, *J* = 8.8Hz, 1 H, Ar-H), 6.73 (dd, *J* = 2.8Hz, 8.8Hz, 1 H, Ar-H), 6.93 (d, *J* = 2.8 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75MHz, $CDCl_3$): δ = 28.84, 29.44, 30.16, 41.73, 52.94, 55.97, 62.57, 65.96, 76.24, 114.73, 116.46, 116.51, 121.72, 139.20, 152.62 ppm. MS (ES+): m/z = 264.2 $[M + 1]^+$.

R = p-Br, **3-(8-bromo2, 3, 3a, 4, 5, 9b–hexahydrofuro[3,2-c]quinoline-4-yl)propan-1-ol (3m, 4m).** Viscous oil.

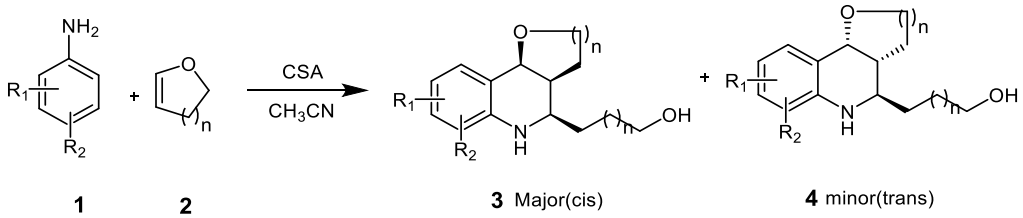
Compound 3(m) Cis-isomer: ^{1}HNMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 1.98 (m, 1 H), 2.61 (m, 1 H), 3.44 (m, 1 H), 3.72 (m, 2 H), 3.80 (m, 2 H), 5.04 (d, *J* = 7.6 Hz, 1 H), 6.42 (d, *J* = 8.8Hz, 1 H, Ar-H), 7.11 (dd, *J* = 2.4Hz, 8.8Hz, 1 H, Ar-H), 7.40 (d, *J* = 2.4Hz, 1 H, Ar-H) ppm.^{13}CNMR (75MHz, $CDCl_3$): δ = 24.03, 29.17, 30.97, 42.38, 52.33, 62.58, 66.90, 75.50, 110.20,116.36, 124.75, 131.21, 132.66, 144.10 ppm.

Compound 4(m) Trans isomer: ^{1}HNMR (300MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 1.98 (m 1 H), 2.21 (m, 1 H), 2.81 (m, 1 H), 3.80 (m, 2 H), 3.95 (m, 2 H), 4.53 (d, *J* = 5.6 Hz, 1 H), 6.58

(d, *J* = 8.8Hz, 1 H, Ar-H), 7.18 (dd, *J* = 2.8Hz, 8.8Hz, 1 H, Ar-H) 7.47 (d, *J* = 2.4Hz, 1 H, Ar-H) ppm.^{13}CNMR (75MHz, $CDCl_3$): δ = 28.81, 29.33, 30.13, 42.26, 52.19, 62.68, 65.84, 75.44, 109.57, 116.60, 122.45, 131.72, 133.54, 144.18 ppm.MS (ES+): m/z = 312.2 $[M + 1]^+$

Result and Discussion

This reaction is categorized as ABB' type multi-component reaction because cyclic enol ether (B) component is chemo differentially incorporated in two distinct manners (B and B'). Chemo differentiating term signify that each chemical function incorporated into the product is chemically different from the other. The cyclic enol ether serves as dual role in Multicomponent Povarov reaction, acting as an electron rich dienophile and as an aldehyde in the formation of Schiff base. The ABB' is a particular type of cycloaddition reaction which reflects unambiguously the dual role played by component B (B and B') to ensure the complexity and functional diversity of the final product. The reaction of aromatic amine (1.0mmol) with Cyclic enol ether (2.0mmol) in the presence of 30% CSA in acetonitrile at room temperature furnished the corresponding pyrano and furanoquinoline 3 and 4 in good to excellent yield.



Scheme1: Synthesis of pyrano and furanoquinoline.

The reaction involves coupling of an electron rich alkene (cyclic enol ether) with an N-arylimine (derived from aniline and an electron rich alkene) by a process that may occur as a concerted inverse electron demand Diels-Alder mechanism or via a stepwise "mannich-like" pathway. Based on this hypothesis Camphor sulfonic acid was used for catalyzing 1:2 coupling of substituted anilines with electron rich alkene such as 3,4-dihydro-2H-pyran or 2,3-dihydrofuran to give highly functionalised pyrano and furanoquinolines. The Cis and Trans isomers are formed in almost all the cases. However, in the Camphor sulfonic acid promoted reaction Cis isomer is preferentially formed with high diastereoselctivity. Furanoquinolines showed better diastereoselectivity than pyranoquinolines. The reaction condition and catalyst loading were optimized taking aniline and 3,4-dihydro-2H-pyran as model. The reaction of aniline with pyran in the presence of 5 mole % Camphor sulfonic acid in CH_3CN only trace amount of desired product is formed in 24 h. To optimize the best reaction condition, we carried out reaction with 5, 10, 20, and 30 mole % of Camphor Sulfonic Acid. The best result was obtained with camphor sulfonic acid (30 mol %) in terms of yields and reaction time.

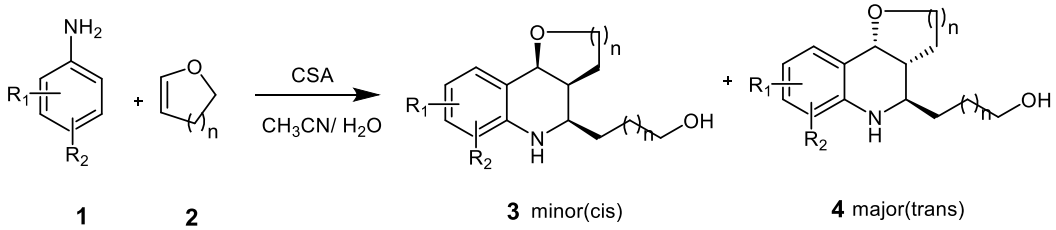
Table-1: Reaction optimization with organocatalyst and solvent

Organo-catalyst	Mole	Solvent	Time (h)	Yield[a] (%)	Cis/trans[b]
Citric Acid	30%	CH_3CN	9	45	55: 45
Tartaric acid	30%	CH_3CN	10	50	60: 40
PTSA	30%	CH_3CN	8	60	65: 35
CSA	0%	CH_3CN	48	-	-
CSA	5%	CH_3CN	24	trace	-
CSA	10%	CH_3CN	8	20	-

CSA	20%	CH_3CN	8	56	75: 25
CSA	30%	THF	8	58	68: 32
CSA	30%	DMF	8	50	60: 40
CSA	30%	CH_3CN	4	80	85:15
CSA	30%	THF-H_2O	8	65	48: 52
CSA	30%	DMF-H_2O	8	50	50: 50
CSA	30%	CH_3CN-H_2O	4	80	35:65

We also carried out blank reaction (catalyst free) with aniline and 3,4-dihydro-2H-pyran at room temp in CH_3CN for 3 days but no reaction was observed. In order to see solvent effect on this reaction, we performed reaction in acetonitrile, DMF, THF, THF/H_2O (7:3), and acetonitrile/ H_2O (7:3). Acetonitrile was found to be the best solvent regarding yields, reaction time and selectivity. Interestingly, when water is used along with acetonitrile and THF diastereoselectivity was switched towards trans. (Scheme 2) We have carried out reaction with Citric acid, tartaric acid, PTSA and CSA as catalyst, but the diastereoselectivity was poor in all cases in comparison to CSA. However, PTSA gave better results in comparison to citric acid and tartaric acid (Table1).

Reaction of aniline with 3,4-dihydro-2H-pyran in acetonitrile in the presence of camphor sulfonic acid (30 mol%), gave Pyranoquinolines in good yield (80%) with high cis selectivity. (Table1). 3a (Cis product) was obtained as major product whereas 4a (Trans product) was obtained as minor. The assignment of Cis diastereomer was based on comparison to similar compounds and the H5-H6 and H7 coupling constants (typically J-H5_H6 = 5-7 Hz and J-H6_H7 = 6-7 Hz). The optimized condition for pyranoquinolines was applied for the synthesis of furanoquinolines. The selectivity and yield were better than corresponding pyranoquinolines. Subsequently a series of substituted anilines were reacted with cyclic enol ether to give 2-(hydroxyalkyl) pyrano and furanoquinoline derivatives. Pyranoquinoline 3(Cis) and 4(Trans) were obtained in varying ratio derived from different substituted anilines. The substituent on aniline has a marked effect on the reaction. Aniline with electron donating group favours reaction more than electron withdrawing group. The results of this study are shown in (Table 2). A proposed mechanism for the formation of furanoquinolines is given in figure 1.



Scheme 2: Synthesis of furanoquinolines.

Table2: Organocatalyzed formation of pyrano and furanoquinoline

Reaction condition: 1mmol (aromatic-amine) 2mmol (cyclic enol ether) [a] isolated yield. [b]

Entry	R_1	R_2		Reaction time (h)	Yield[a] (%)	Cis/trans[b]
a	H	H	2	4.0	80	85:15
b	H	p-	2	4.5	74	79:21
c	H	o-	2	4.0	85	82:18
d	H	p-	2	5.5	83	80:20
e	H	p-F	2	6.0	72	75:25
f	H	p-Cl	2	5.0	65	78:22
g	H	p-Br	2	6.5	79	92:08
h	H	m-	2	5.5	65	90:10
i	H	H	1	4.5	78	75:25
j	H	p-Cl	1	6.0	95	95:05
k	H	p-	1	4.5	90	90:10
l	H	p-	1	4.0	89	89:11
m	H	p-Br	1	4.4	90	96:04

cis-trans ratio determined by ^{1}H NMR.

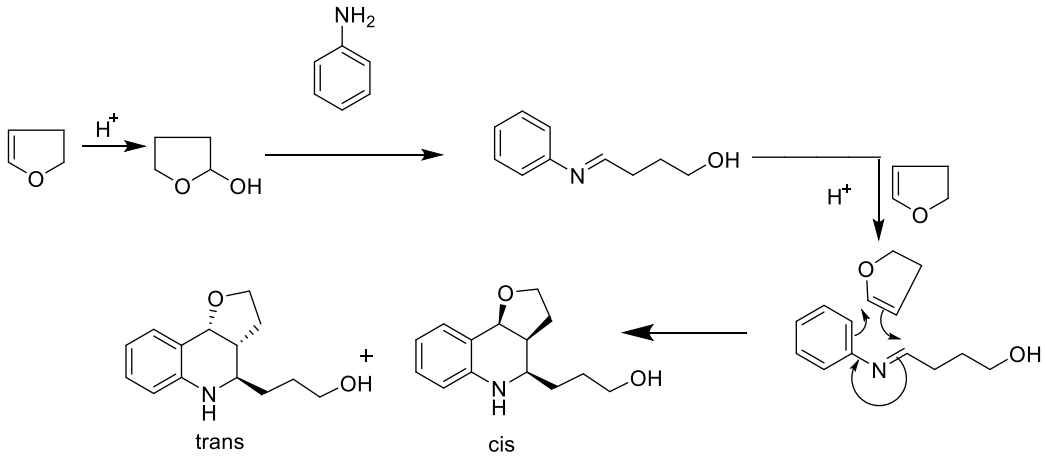


Figure 2: Proposed Mechanistic Pathway

In order to further study, the finding of shifting diastereoselectivity with the use of water as cosolvent, we have carried out several reactions in water–acetonitrile system. Interestingly in all the reaction diastereoselectivity is switched towards trans with the use of water as cosolvent. (Table 3) The possible explanation of shift in diastereoselectivity may be because 2-hydoxy tetrahydropyran or 2-hydroxy tetrahydrofuran reacts with aromatic amines in water–acetonitrile system instead of 3, 4-dihydropyran or 2, 3-dihydrofuran. We further performed reaction in LiCl, and Guanidinium chloride with water as cosolvent. Lithium chloride is a salt which increases the hydrophobic effect i.e. "Salt Out'' as expected from this we get an increase diastereoselectivity as well as increase in rate of reaction. Guanidinium chloride decrease the

hydrophobic interaction i.e. "Salt In'' does not increase the rate of reaction but side product was also formed

Table-3: Camphor sulfonic acid catalysed synthesis of pyrano/furanoquinoline in CH_3CN-Water system.

Entry	R_1	R_2		Time (h)	Yield[a] (%)	Trans/cis[b]
a	H	H	2	4.0	80	55:45
b	H	p-OCH_3	2	4.5	74	79:21
c	H	o-OCH_3	2	4.0	85	82:18
d	H	p-CH_3	2	5.5	83	80:20
e	H	p-F	2	6.0	72	75:25
i	H	H	1	4.5	78	75:25
l	H	p-OCH_3	1	4.0	89	89:11
m*	H	p-OCH_3	2	3.5	76	84:16
n**	H	p-OCH_3	2	4.5	56	70:30

Conclusion

In summary we have developed Camphor sulphonic acid catalyzed multicomponent synthetic methodology for preparation of pyrano and furanoquinolines. The developed methodology involves highly diastereoselective synthesis of pyrano/furanoquinolines by the reaction of aromatic amines with cyclic enol ether using camphor sulfonic acid as an organocatalyst at ambient temperature. The proposed synthetic route not only provide an alternative to access quinolone moieties but also proved to a sustainable protocol for synthesis of heterocyclic structures. Diastereoselectivity observed in said protocol is the key point in our developed process.

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